REMARKS

Applicants have amended claim 1 to expedite prosecution. Support for this amendment can be found throughout the specification, and particularly, Figure 2 and the accompanying text.

Applicants have written claims 3 and 4 in an independent form.

Applicants have amended claims 8, 9, 13, 14, and 15 to depend on claims 3 and 4, instead of claim 1.

Applicants have added a new claim 17. Support for this amendment can be found throughout the specification and, particularly, for example at page 9, second full paragraph.

Accordingly, all the amendments are supported by the specification as filed and do not introduce new matter and their entry is respectfully requested. At a minimum, the amendments should reduce the issues for appeal.

Claims 1, 3-5, 7-16 were rejected under 35 U.S.C. 103(a) as being unpatentable over Beug et al., Chaudhary et al. and Wu et al.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

The present invention provides a delivery system and method for selective delivery of a nucleic acid to a specific population of target cells.

This is accomplished by use of a **fusion** protein comprising (1) a nucleic acid binding protein, such as protamine, and (2) an antibody (claim 1) or a single chain antibody (claim 4) which specifically recognizes a cell surface marker on the desired target cell. The nucleic acid is joined to this complex by its interaction with the nucleic acid binding portion of the fusion protein. The fusion protein of the present invention is formed as one protein with one amino and one carboxyl terminal end, thereby eliminating problems with the use of chemical conjugation of two proteins.

The Examiner has contended that the invention as limited by the present claims is no different from what is taught in Wu and Beug. Applicants respectfully disagree, because the combination of these three references does not teach the fusion protein of any of the present claims.

Applicants have made explicit that which was implicit that the present invention is based upon an improvement to the chemical conjugation of two separate proteins as taught by the cited references.

Accordingly, amended claim 1 makes clear that the fusion protein consists of an antibody and a nucleic acid binding protein with one N- and one C-terminal end. Neither Wu nor Beug nor Chaudhary teach or suggest such a fusion protein to deliver nucleic acids into cells.

Both Wu and Beug teach protein conjugates that are aggregates formed from two separate proteins and consequently, the conjugate contains a **mixture of two proteins** with **two amino** and **two carboxyl terminal ends**. Wu used a chemical conjugate approach as depicted in Figure 1, consisting of a nucleic acid bound to a polycation, which is itself covalently bound through disulfide bond to a ligand. Also Beug used a chemical conjugate approach, not a fusion protein, described as "a transferrin-polycation conjugate" in the abstract, lines 3-4, for delivery of a nucleic acid. Thus, Beug does not suggest the present invention's fusion proteins, and in fact specifically teaches away from such an approach. While fusion proteins necessarily use a fixed ratio comprising one targeting moiety for each nucleic acid binding moiety (i.e. 1:1), Beug teaches the advantages of being able to vary these two components from ratios of 1:4 up to 10:1, a 40-fold range. Thus, nothing in Beug provides the artisan with any motivation or suggestion that a fixed 1:1 ratio is preferable.

Similarly, Wu teaches the use of chemical conjugates, and uses "ligands" to target cells. While both Wu and Beug refer to antibodies in passing, neither focuses on antibodies, particularly single chain antibodies, in any way, including discussing the specific advantages they offer. The Examiner has stated that it was well known in the art that using an antibody gives the "most specific and versatile targeting of any antigen." Both systems were looking at targeting receptors with a ligand and there is no reason why an antibody would be better.

The Examiner states at page 4, lines 2-3, that "Wu et al. clearly teach the combination of a cell targeting protein with a nucleotide molecule as one **fusion** protein"[emphasis added]. However, Wu does not once recite the term "**fusion**." This is not a coincidence. "Fusion protein" is commonly understood as one protein with one N- and C-terminus. "**Conjugate**" is a combination of two separate proteins. There are real differences between such approaches. This was discussed by Dr. Marasco in addressing the Li et al. reference.

Applicants respectfully submit that the Declaration of Dr. Marasco discussing Li et al. also shows the differences between a fusion protein as claimed here and a chemical conjugate as taught by both Wu and Beung. Dr. Marasco is both a co-inventor of the present invention and a co-author of Li, and thus is in a unique position to describe what the experiments reported therein mean.

The Examiner has ignored the expert testimony of the declarant and argues against the scientific judgment of the expert. Moreover, the Examiner **inappropriately** cites to In re Wood in this context. Wood discussed lawyer's argument. However, the statements made here are not the lawyer's but the co-author's and co-inventor's, who is an expert in the field, and they are based on his personal experience of the experiments presented to the examiner. The Examiner states that "[u]pon examination of the experiments represented by the two figures referred to by Applicants, it is found that Applicants conclusion of surprising results can not be made." (Feb. 4 Office Action, p. 5, lines 18-19)

Figure 6C shows the fusion protein approach, while Figure 7B uses the chemical conjugate approach. The Examiner's statement ignores what the results of both figures teach.

As indicated in Li, and explained in Dr. Marasco's Declaration, paragraph 18, it is absolutely appropriate to compare Figure 6C with Figure 7B. Both experiments use the same antibody, an antibody specific for ErbB2 receptor, which is expressed on the surface of SKBR3 cells but is not expressed on the surface of MCF7 cells. Thus, one would expect this antibody to preferentially target SKBR3 cells. Furthermore, both experiments use the same reporter gene, detected by measuring luciferase activity. Given that these experiments use the same target cells, the same antibody, and the same nucleic acid for delivery, comparison of their results is entirely appropriate.

These two experiments clearly show the increased selectivity afforded by the fusion protein approach for targeted nucleic acid delivery.

Nor is Dr. Marasco's finding of differences between these two approaches an isolated finding. See, for example, the review by Yan and Marriott, Current Opinion in Chemical Biology, 2003, 7 at p. 637, submitted herein (as Exhibit A), where they provide a discussion about pros and cons of protein conjugates versus fusion proteins in the context of fluorescent protein labelling. This confirms that differences in results can and do occur.

While Chaudhary does use a fusion protein, their system is not for delivering nucleic acids. The fusion protein of Chaudhary delivers a protein (an immunotoxin), to a specific cell type; Chaurdhary does not deliver nucleic acid and does not teach such a system. Accordingly, in view of the fact that the references to delivering nucleic acids both teach a chemical conjugate and see no problems with such an approach, there is no motivation in the combination to use a fusion protein to deliver nucleic acid.

Accordingly, the rejection of claim 1 should be withdrawn.

Amended claim 3 is directed to fusion proteins having an antibody directed to a viral envelope protein, a cellular receptor, or an extracellular domain of an activated receptor, as the cellular targeting portion of the fusion protein. None of the cited references teach using an antibody to a viral envelope protein, a cellular receptor, or an extracellular domain of an activated receptor, as the cellular targeting portion of the fusion protein in delivering a nucleic acid to the cell.

Amended claim 4 is limited to fusion proteins that have a single chain antibody as the antibody portion. None of the cited references teach or suggest a system where a fusion protein comprising an antibody is a single chain antibody.

Applicants respectfully submit that the present application was filed in 1993, and that the art must be considered in light of what was known at the time of filing. The inventors are the first to report successfully using fusion proteins in the delivery of nucleic acids. This system is a significant and unexpected improvement upon the chemical conjugation. Moreover, Applicants used a single chain antibody – the subject of claim 4– which is superior to a whole antibody for nucleic acid delivery.

Applicants are also submitting an article, Song et al., where Dr. Marasco, a co-inventor of the present invention, is a co-author (as Exhibit B). Song shows a vast improvement in RNA cell delivery when using the method of the present invention. This article, published in 2005, discusses the problems with conventional nucleic acid delivery systems as applied to siRNA delivery. In contrast, Song finds that the method presented by the Applicant works as a solution to their problem in targeted delivery of siRNAs. Song further explains the specific advantages of using single chain antibody instead of a whole antibody, such as that single chain antibody does not trigger an undesired interferon response (page 5, left column, first paragraph).

Thus, the rejection of the claims should be withdrawn.

Claim 6 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Beug et al. in view of Chaudhary et al. and Wu et al as applied to Claims 1, 3 – 5, and 7 – 16, and further in view of Ryder et al.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

Applicants respectfully submit that the addition of Ryder et al. to the combination in no way overcomes the essential deficiency of the references discussed above. Ryder in no way discloses using such nucleic acid binding domain to deliver nucleic acids to cells as part of a fusion protein, nor provides any motivation to the skilled artisan to consider such system. Thus, Ryder cannot cure the fundamental defect in the original combination of references, which do not teach the use of an antibody fusion protein for selective delivery of a nucleic acid.

Accordingly, for the reasons of record which are repeated herein, and for the reasons mentioned above, this rejection of the claims should also be withdrawn.

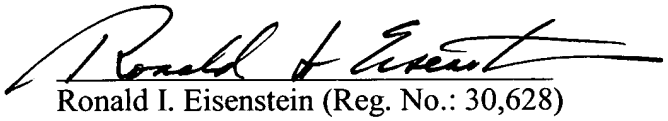
Accordingly, Beug et al., Chaudhary et al. and Wu et al. teach nothing whatsoever of the claimed method. Thus, the rejection should be withdrawn.

In view of the foregoing arguments and amended claims, Applicants respectfully submit that all claims comply with 35 U.S.C. §103(a).

In view of the foregoing, applicants respectfully submit all claims are in condition for allowance. Early and favorable action is requested.

Respectfully submitted,

Date: 6/6/05



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